REMARKS

Reconsideration of the above-identified application is requested in view of the following remarks.

1. Claims

Claims 113, 116-125 and 145-156 are pending.

2. 35 USC 112, first paragraph: Written Description

Claims 113, 116-125 and 146-156 stand rejected as failing to comply with the written description requirement. Applicants traverse this rejection.

The Examiner states that the rejection is maintained "because the instant generic claims, 113 and 116, recite 'comprising' language that reads on any polypeptide having within its amino acid sequence a region consisting of either SEQ ID NO:6 or 7", and that such a genus of polypeptides "was not described or envisioned at the time of application filing". In support of this rejection, the Office Actions of 31 Aug 07 and 18 Jan 07 put forth the following:

(i) "the claims are drawn to a genus of polypeptides that was not described or envisioned at the time of application filing"; (p. 4, 31 Aug 07)

(ii) "(t)he specification teaches a total of three HER2 proteins" (full length HER2/neu protein of SEQ ID NO:1, 919 amino acid SEQ ID NO:6, and 712 amino acid SEQ ID NO:7); (see p. 4, 31 Aug 07 and p. 8, 18 Jan 07)

(iii) "the specification does not disclose or contemplate any other proteins containing amino acid residues of SEQ ID NO:6 or 7"; (p. 4, 31 Aug 07; p.8, 18 Jan 07)

(iv) "the claims encompass a genus of proteins defined solely by a principal structural property, namely that the protein contain a stretch of amino acids of SEQ ID NO:6 or 7, which is simply a wish to know the identity of any material with that structural property"; (p. 8, 18 Jan. 07)

(v) "relevant identifying characteristics of the genus such as structure or other physical and/or chemical characteristics of a 'protein' are not set forth in the specification as filed" ; (p. 8, 18 Jan 07).

Statement (i) is a conclusion. MPEP 2163.04 notes that if the examiner concludes that the disclosure does not reasonably convey that the inventor had possession of the invention, "the examiner has the initial burden of presenting evidence or reasoning to explain why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims."

Applicants submit that the Examiner's rationale as shown in (ii) – (v) do not provide sufficient evidence or reasoning to explain why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims.

Regarding statement (ii) ("the specification teaches a total of three HER2 proteins"): Applicants agree that the specification provides the three sequences noted by the Examiner (full-length human HER2/neu protein (SEQ ID NO:1); 919 amino acid sequence consisting of the human ECD and the PD (SEQ ID NO:6); 712 amino acid sequence consisting of the human ECD and the ΔPD truncated phosphorylation domain (SEQ ID NO:7)). Applicants dispute that that the specification *only* teaches these three HER2 proteins (see for example, rat HER2 SEQ ID NOs: 2 and 8, and mouse HER2 SEQ ID NO: 14; see discussion on pages 13 and 19 of various ECD-ICD constructs, including ECD-PD constructs).

Regarding statement (iii) ("the specification does not disclose or contemplate any other proteins containing amino acid residues of SEQ ID NO:6 or 7", underlining added). Applicants first note that the claims recite polypeptides (not proteins) comprising SEQ ID NO:6 or 7. The specification discloses multiple polypeptides comprising SEQ ID NO:6 or 7, e.g. at page 22 regarding polypeptides of SEQ ID NO:6 or 7 fused to unrelated immunological peptides (see pages 22-23, regarding use of protein D, LYTA, Ra12, etc). Example 9 describes the expression in *E. coli* of a mouse ECD-PD construct fused to the Ra12 fragment of *M. tuberculosis*.

Applicants would appreciate receiving clarification on why the Examiner believes one skilled in the art would not recognize that the inventors were in possession of polypeptides comprising SEQ ID NO:6 (or 7) and a non-HER2 fusion partner, such as those described in pages 22-23 and Example 9 of the specification.

Statements (iv) and (v) were made in the Office Action of 18 Jan 07. Applicants addressed these statements in the Response dated 13 June 2007, where Applicants outlined how the specification sets forth both the structure and function of the claimed polypeptides (see last paragraph of page 7, continuing to page 8 of 13 June 2007 Response).

In response, the Examiner merely states (see page 5, 31 Aug 07 Office Action) that "Applicants statement of record supports the Examiner's position that the polypeptide consisting of SEQ ID NO:6 or 7 would meet the requirements under 35 USC 112." However, this is not the issue at hand. Applicants agree that the specification provides written description support for a polypeptide consisting of SEQ ID NO:6 or 7. But the specification also supports the claims to polypeptides comprising SEQ ID NO:6 and 7, and the Examiner has not refuted this position. The Examiner has not provided evidence or reasoning that is contrary to Applicants' position, and in some cases appears not to have considered certain parts of the specification (e.g., disclosure of fusion proteins containing SEQ ID NO:6 or 7 and other proteins such as Ra12 or protein D; disclosure of various HER2 proteins).

Applicants maintain that a prima facie case has not been established for the present rejection, and request withdrawal.

3. Rejection under 35 USC 112, second paragraph: Indefiniteness

Claims 113, 116-125 and 146-156 stand rejected as indefinite. Applicants traverse this rejection.

The Examiner states that the claims are indefinite "because it is unclear if SEQ ID NO:6 or 7 is administered, or a polypeptide comprising SEQ ID NO:6 or 7. Rewriting the claims to recite that the respective composition or the polypeptide comprising the composition (*sic, the sequence?*) is administered in an immune response eliciting or enhancing amount could overcome the rejection." (Office Action, page 7 -8)

Independent claims 113 and 116 recite a method for eliciting or enhancing an immune response to HER-2/neu protein in a warm-blooded animal, the method comprising administering a composition comprising a polypeptide, where the polypeptide comprises the amino acid sequence of SEQ ID NO:6 [or 7]. The claims further state that said SEQ ID NO:6 [or 7] is administered in an amount effective to elicit or enhance the immune response

to HER-2/Neu. Thus claim 113 recites (a) administering a composition, where (b) the composition comprises a polypeptide, and (c) the polypeptide comprises SEQ ID NO:6. Administering the composition necessarily administers the polypeptide; administering the polypeptide necessarily administers SEQ ID NO:6. As discussed in Applicants' previous response (13 June 07), SEQ ID NO:6 is capable of eliciting an immune response to HER-2/neu (see also specification at last paragraph on page 12 continuing to p. 13; pages 15-16). Claim 113 recites that SEQ ID NO:6 is administered in an amount effective to elicit or enhance the immune response to HER-2/Neu to indicate that, in administering the composition, a sufficient amount of SEQ ID NO:6 is administered to cause the desired immune response.

The claim does not recite administering a composition to enhance HER-2/neu immune reaction, where the immune response is due solely to some component *other than* SEQ ID NO:6 (or 7). The structure of SEQ ID NO:6 and the function of eliciting an immune response are related; the claimed method requires administering sufficient SEQ ID NO:6 (structure) to elicit an immune response to HER-2/neu (function). The administered composition must comprise sufficient SEQ ID NO:6 to induce an immune reaction to SEQ ID NO:6 (i.e., an immune reaction to the ECD and PD of HER-2/neu).

As stated in MPEP 2171, the requirement for definite claims is an objective one; it is not dependent on the views of applicant or any particular individual, but is evaluated in the context of whether the scope of the claim is clear to a hypothetical person possessing the ordinary level of skill in the pertinent art. The primary purpose of the definiteness requirement for claim language is to ensure that the scope of the claims is clear so the public is informed of the boundaries of what constitutes infringement of the patent. (MPEP 2173). Applicants may use functional language or any style of expression or format of claim which makes clear the boundaries of the subject matter for which protection is sought. As noted by the court in *In re Swinehart*, 439 F.2d 210, 160 USPQ 226 (CCPA 1971), a claim may not be rejected solely because of the type of language used to define the subject matter for which patent protection is sought. (MPEP 2173.01)

Applicants submit that one of ordinary skill in the relevant art would understand that the claims contemplate administering a composition comprising elements in addition to a polypeptide of SEQ ID NO:6 (see for example, dependent claim 118 reciting that the

composition contains a physiologically acceptable carrier), but that the claims require that SEQ ID NO:6 be administered in an amount sufficient to cause the recited effect.

Withdrawal of the present rejection is requested.

4. Rejection under 35 USC 112, first paragraph: Enablement

Claims 113, 116, 155 and 156 stand rejected as lacking enablement for using the method to elicit or enhance an immune response in a human. Applicants dispute this rejection, and maintain that the Examiner has not made a *prima facie* case of non-enablement.

The present claims recite eliciting or enhancing an immune response to HER-2/neu protein. The Examiner has acknowledged that the specification is enabling "for methods of eliciting an immune response using a HER-2/neu fusion protein comprising SEQ ID NO:6 or 7 to stimulate T-cell proliferation and cytotoxicity, and to induce B cells to produce an antibody, for use in treating malignancies such as breast, ovarian, colon, lung and prostate cancer" (see Office Action 18 Jan 07, page 9). However, the Examiner then states that the specification "does not reasonably provide enablement for using the method to elicit a specific prophylactic or therapeutic immune response for any disease or disorder in a human." This is not the proper measure of enablement given the present claims.

Applicants submit that the Examiner is requiring applicants to show enablement of a clinical treatment (prophylactic or therapeutic treatment for a human disease), rather than to show enablement of the claimed method (method of eliciting or enhancing immune response to HER2). As noted in MPEP 2164, "to comply with 35 U.S.C. 112, first paragraph, it is not necessary to 'enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect.' *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1338, 68 USPQ2d 1940, 1944 (Fed. Cir. 2003)"

The Examiner has not provided technical reasons or evidence in support of the non-enablement conclusion. Rather, the Examiner has merely cited a lack of working examples in the specification and concluded that undue experimentation would be required. The Office Action dated 18 Jan 07 states "absent a specific and detailed description" in the specification of "how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for eliciting

or enhancing a specific preventative or therapeutic immune response in a human", the claims are not enabled. Yet the claims do not recite provision of a preventative or therapeutic immune response in humans.

(a) Kurebayashi article

Applicants response of 13 June 07 referred to a review article by Kurebayashi (*Breast Cancer* 8(1):45 (Jan 2001)) as evidence of the state of the art at the time the specification was filed. The Kurebayashi article describes the HER2 signaling pathway, the oncogenic potential of HER2 overexpression, and HER2 overexpression as a therapeutic target (see e.g., page 49, end of first column continuing to second column). In response, the Examiner states that "Kurebayashi predicts that vaccines will promote immunity to HER2 but specifically states that it is unknown whether immunity to HER2 predicts improved survival"[1]. The Examiner continues "taken alone, Kurebayashi is not persuasive evidence that an attenuated[2] form of HER2 as recited in the instant claims could generate or enhance an immune response in a human".

Applicants first note that Kurebayashi should not be taken alone, but considered in view of all the evidence on the record and the standards of patentability under Title 35 of the USC. The Examiner has already stated that the specification is enabling for methods of eliciting an immune response using a HER-2/neu fusion protein comprising SEQ ID NO:6 or 7 to stimulate T-cell proliferation and cytotoxicity, and to induce B cells to produce an antibody (OA 18 Jan 07, page 9).

Further, Kurebayashi's comment regarding "improved survival" is not evidence that the claimed method is non-enabled under the standards of Title 35. The present claims do not recite "improved survival".

In re Brana 34 USPQ2d 1436, 1442 (Fed. Cir. 1995, underlining added) states "Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which

[1] The full quote is: "It is not yet known whether immunity to HER2 predicts improved survival, but existent immunity predicts that vaccines will be able to promote immunity to HER2. Effective immunization regimens of active immunotherapy have been explored."

[2] Applicants note that "attenuated" is the Examiner's description; neither the present specification nor claims uses the word "attenuated".

an invention in this field becomes useful is well before it is ready to be administered to humans." The court continues: "At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant prove regarding the practical utility or usefulness of the invention for which patent protection is sought." (*Id.*) The court continues, stating "The Commissioner, as did the Board, confuses the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption. See Scott v. Finney,34 F.3d 1058,1063, 32 USPQ2d 1115, 1120 (Fed.Cir. 1994)."

The Examiner further states that Kurebayashi is not persuasive evidence of "what an effective amount would be for achieving this endpoint" (OA 31 Aug 07, page 5). However, as discussed in MPEP 2164.01(c): "(I)t is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation. If one skilled in the art, based on knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or method of use without undue experimentation, this is sufficient to satisfy 35 USC 112, first paragraph. The applicant need not demonstrate that the invention is completely safe."

The Examiner has not provided evidence and/or reasoning in support of the contention that it would require undue experimentation by one skilled in the art to define an effective amount for the claimed methods. Dose-escalation studies are well-known in the art, as is the ability to measure immunological end-points (such as T-cell proliferation and cytotoxicity, production of specific anti-HER2 antibodies). The specification describes pharmaceutical compositions and routes of administration suitable for use in humans (see e.g., paragraphs 0011, 0206-0212). Various methods of detecting an immune response to HER2 are described, e.g. at paragraphs 0223 - 0236 of the specification.

Applicants submit that the Examiner's view of Kurebayashi does not provide the needed technical reasons or evidence to support the non-enablement conclusion.

(b) Limentani references and Declaration of Dr. Louahed

Applicants Response dated 13 June 07 referred to an Abstract by Limentani et al.[3] (the ASCO abstract), a Poster by Limentani et al[4], and included a Rule 132 Declaration by Dr. Jamila Louahed (an author on both the ASCO Abstract and the Poster).

The ASCO Abstract reports on a dose escalation study (GSK Study ID 719125/002 (National Clinical Trials identifier NCT00058526)) of a recombinant HER2 protein, used as an adjuvant treatment for Stage II or Stage III Her2 positive breast cancer in human patients. The Limentani Poster reports on the same study as the Abstract, as well as a Phase II study of metastatic HER2 positive breast cancer in human patients (GSK Study ID 100633 (National Clinical Trials Identifier NCT00140738)).

The Louahed Declaration identified both the ASCO Abstract and the Poster (paragraphs 2 and 4), and noted that the references report data from clinical studies of a recombinant HER2 protein as an adjuvant in treating HER2 positive breast cancer (paragraphs 3 and 5). Paragraph 6 noted that Dr. Louahed reviewed the present specification and the 919-amino acid sequence of SEQ ID NO:6. At paragraph 7, Dr. Louahed states that the recombinant HER2 protein referred to in the Abstract and the Poster, and used in the reported studies, was the 919 amino acid sequence disclosed as SEQ ID NO:6 in the specification.

These post-filing publications were cited as evidence of the level of skill in the art as of the application filing date, and as evidence that the method disclosed in the application is enabled by the specification. The Declaration was submitted to establish that the materials used in the reported clinical studies were commensurate to what was disclosed in the specification.

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[3] Limentani et al., *Journal of Clinical Oncology*, 2006 ASCO Annual Meeting Proceedings, Vol. 24, No. 18S (June 20 Supplement), 2006:631

[4] The 31 Aug 07 Office Action states (page 6) that a copy of the Limentani Poster was not provided by Applicants in the Response of 13 June 07. However, the IDS submitted therewith lists the Poster (item number 6) and is indicated as reviewed by the Examiner. For convenience, an additional copy of the poster is submitted herewith. Citation: Limentani et al., presented at the 18th EORTC-NCI-AACR Symposium, Nov. 7-11 2006 , Prague, CZ (conference organized by the European Organization for Research and Treatment of Cancer (EORTC) in conjunction with the National Cancer Institute (NCI) and the American Association for Cancer Research (AACR))

In response, the Examiner focuses on the disparate terminology used in the references and the specification, while ignoring the factual statements made by Dr. Louahed that the ECD/ICD constructs of the references were SEQ ID NO:6.

The Examiner contends that an ECD/ICD polypeptide (as referred to in the references) "would not correspond to an ECD/PD polypeptide of SEQ ID NO:6." In support of this contention, the Examiner notes that:

> On p. 7 of the specification, an ECD/ICD fusion protein is specifically defined as 'comprising the extracellular domain and the intracellular domain of the Her2/neu protein' and that and that an 'ECD/ICD protein does not include a substantial portion if any of the HER2/neu transmembrane domain.' Then in the next paragraph, the ECD/PD or ECD/ΔPD is specifically defined as 'comprising the extracellular domain and phosphorylation domain' and that an ECD/PD and ECD/ ΔPD does not include a substantial portion if any of the HER2/neu transmembrane domain.' In the center of p. 8 of the Response of 6/28/07, Applicants specifically refer to fusion proteins combining ECD with PD as the preferred form. Based on these definition of record and absent further evidence to the contrary, it is not understood how the 'ECD/ICD' protein of the Limentani abstract could be the same as the 919 amino acid sequence of SEQ ID NO:6.
> (Examiner's remarks, Office Action dated 31 Aug 07, page 6)

Applicants do not agree with the Examiner's view of how the specification defines ECD/ICD and ECD/PD polypeptides. The specification at page 7 states that an ECD/ICD polypeptide comprises the extracellular domain and the intracellular domain or fragments thereof but does not contain a substantial portion (if any) of the transmembrane domain. An ECD/PD polypeptide is described (still on page 7) as polypeptides comprising the extracellular domain and the phosphorylation domain but not containing a substantial portion (if any) of the transmembrane domain. As noted on page 7 (e.g., in first full paragraph), the PD is found within the ICD, thus the PD is a fragment of the ICD. From the specification as a whole, it is clear that ECD/PD polypeptides are a subset of ECD/ICD polypeptides. SEQ ID NO:6 is a specific ECD/PD polypeptide, and is also an example of a polypeptide consisting of the ECD and a fragment of the ICD (where the fragment is the PD). The Examples in the specification refer to specific ECD/PD polypeptides.

The Limentani Abstract describes a recombinant HER2 protein that included the extra-cellular domain and part of the intra-cellular domain of HER2, and refers to this as an ECD/ICD polypeptide.

The Examiner states (p. 7, 31 Aug. 07) that "the newly submitted evidence appears to contradict the disclosure in the specification … based on the totality of the evidence." However, any 'contradictions' between the terminology used in the Limentani references and that of the specification is specifically addressed by Dr. Louahed's factual declaration. Dr. Louahed states (para 7) that the recombinant HER2 protein used in the studies described in the Limentani references was the 919 amino acid sequence of SEQ ID NO:6. Applicants request that the Examiner review the specification, the references, and the factual statements of Dr. Louahed's Declaration, in view of the above discussion.

Applicants do not believe that a prima facie case of non-enablement has been established, but nonetheless refer to MPEP 716.01(d) which states that "Facts established by rebuttal evidence must be evaluated along with the facts on which the conclusion of a *prima facie* case was reached, not against the conclusion itself. *In re Eli Lilly*, 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990). In other words, each piece of rebuttal evidence should not be evaluated for its ability to knockdown the *prima facie* case. All of the competent rebuttal evidence taken as a whole should be weighed against the evidence supporting the *prima facie* case. *In re Piasecki*, 745 F.2d 1468, 1472, 223 USPQ 785, 788 (Fed. Cir. 1984)."

As discussed in MPEP 2164, in an enablement rejection "it is incumbent upon the Patent Office … to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971).

The Examiner has not provided technical reasons or sufficient evidence in support of the non-enablement conclusion. Withdrawal of the present rejection is requested.

5. Conclusion

Applicants respectfully submit that the present application is in condition for allowance. If the Examiner believes a telephone conference would expedite prosecution of the application, please do not hesitate to call the undersigned at 919-483-1012.

The Commissioner is hereby authorized to charge any fees required or credit any overpayment to Deposit Account No. 07-1392.

Respectfully submitted,

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Enclosed :

Supplemental copy of **Limentani et al**., A Recombinant HER2 protein evaluated for cancer immunotherapy: induction of specific antibodies and T-cells. (Poster) 18th EORTC-NCI-AACR Symposium, November 7-11, 2006, Prague, CZ